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## RADIOLABELLED-ANTIBODY THERAPY OF B-CELL LYMPHOMA WITH AUTOLOGOUS BONE MARROW SUPPORT

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**Abstract Background.** Radiolabeled monoclonal antibodies recognizing B-lymphocyte surface antigens represent a potentially effective new therapy for lymphomas. We assessed the biodistribution, toxicity, and efficacy of anti-CD20 (B1 and 1F5) and anti-CD37 (MB-1) antibodies labeled with iodine-131 in 43 patients with B-cell lymphoma in relapse.

**Methods.** Sequential biodistribution studies were performed with escalating doses of antibody (0.5, 2.5, and 10 mg per kilogram of body weight) trace-labeled with 5 to 10 mCi of <sup>131</sup>I. The doses of radiation absorbed by tumors and normal organs were estimated by serial gamma-camera imaging and tumor biopsies. Patients whose tumors were estimated to receive greater doses of radiation than the liver, lungs, or kidneys (i.e., patients with a favorable biodistribution) were eligible for therapeutic infusion of <sup>131</sup>I-labeled antibodies according to a phase 1 dose-escalation protocol.

**TREATMENT** with anthracycline-based chemotherapy regimens results in complete remission in 50 to 90 percent of patients with intermediate and high-grade non-Hodgkin's lymphoma and long-term disease-free survival in 30 to 60 percent. Unfortunately, few patients with low-grade lymphoma or relapses of any type of lymphoma can be cured with conventional approaches.<sup>1</sup> High-dose chemoradiotherapy with bone marrow transplantation cures 10 to 50 percent of patients with lymphoma in relapse, but 40 to 80 percent relapse again and 5 to 20 percent die of complications related to transplantation.<sup>2,3</sup> The use of larger doses of chemoradiotherapy has not been feasible because of unacceptable morbidity and mortality.<sup>4</sup>

We hypothesized that prohibitive toxic effects on normal organs might be avoided if larger doses of cytotoxic therapy were selectively targeted to tumor sites with monoclonal antibodies recognizing lymphoma-associated surface antigens. Radionuclides are favorable agents for antibody targeting because isotopes emitting  $\beta$  particles generate radioactive emissions that are tumoricidal over distances spanning several cell diameters, permitting the eradication of antigen-negative tumor cells and diminishing the consequences of inhomogeneous deposition of antibody in

**Results.** Twenty-four patients had a favorable biodistribution, and 19 received therapeutic infusions of 234 to 777 mCi of <sup>131</sup>I-labeled antibodies (58 to 1168 mg) followed by autologous marrow reinfusion, resulting in complete remission in 16, a partial response in 2, and a minor response (25 to 50 percent regression of tumor) in 1. Nine patients have remained in continuous complete remission for 3 to 53 months. Toxic effects included myelosuppression, nausea, infections, and two episodes of cardiopulmonary toxicity, and were moderate in patients treated with doses of <sup>131</sup>I-labeled antibodies that delivered less than 27.25 Gy to normal organs.

**Conclusions.** High-dose radioimmunotherapy with <sup>131</sup>I-labeled antibodies is associated with a high response rate in patients with B-cell lymphoma in whom antibody biodistribution is favorable. (N Engl J Med 1993;329:1219-24.)

tumors.<sup>5</sup> B-cell lymphomas are particularly attractive targets for radioimmunotherapy because of their exquisite radiosensitivity, their well-defined surface antigens, and the availability of multiple monoclonal antibodies to those antigens.

In this report, we describe the results of a phase 1 dose-escalation trial of anti-CD20 and anti-CD37 antibodies labeled with iodine-131 in patients with B-cell lymphoma in relapse. The objectives were to study the biodistribution, toxicity, and efficacy of the antibodies and to estimate the maximal tolerated dose with autologous marrow support.

### METHODS

#### Selection of Antibodies and Patients

The characteristics of the murine monoclonal antibodies used are summarized in Table 1. The antibodies were radioiodinated with sodium [<sup>131</sup>I]iodide (specific activity, 8.0 Ci per milligram) (New England Nuclear) by the chloramine-T method and purified and tested as previously described.<sup>7,8</sup> Patients with B-cell lymphomas expressing the CD20 or CD37 antigen were eligible if they had not responded to conventional systemic therapy, had normal renal and hepatic function, had not been treated for 4 weeks, had no other active medical problems, had an expected survival of 30 days or more, and had lymphoma affecting less than 25 percent of their marrow. Bone marrow was obtained from all the patients and was purged with anti-CD9, anti-CD10, anti-CD19, and anti-CD20 antibodies and complement before cryopreservation. The patients' serum samples were tested for antimouse antibodies as previously described.<sup>7</sup> The protocol was approved by the appropriate institutional review committees, and all the patients gave written informed consent.

#### Biodistribution Studies

During successive weeks, antibodies trace-labeled with <sup>131</sup>I (5 to 10 mCi) were infused intravenously in doses of 0.5, 2.5, and 10 mg per kilogram of body weight together with 0.2 mg of an irrelevant control antibody (DT) trace-labeled with <sup>125</sup>I (3.5 mCi) per kilo-

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gram. Saturated potassium iodide (five drops orally) was administered daily for 30 days (or longer if a therapeutic infusion was given) beginning 24 hours before the antibody infusion. At the completion of each antibody infusion and 48, 96, and 120 hours later, quantitative gamma-camera imaging was performed as previously described.<sup>7,8</sup> Samples of tumor and marrow were obtained by biopsy 24 to 48 hours after most of the infusions for assessment by immunoperoxidase histocytochemical techniques, flow cytometry, and gamma counting. The radioiodine content of the biopsy specimens and serial imaging data were used to estimate with standard dosimetry methods the doses of radiation absorbed by organs, tumors, and the whole body.<sup>9-10</sup>

### Therapeutic Infusions

Patients in whom biodistribution studies demonstrated that every assessable tumor site would receive higher absorbed doses of radiation than the liver, lungs, and kidneys were considered to have a favorable antibody biodistribution and were given single therapeutic intravenous infusions of <sup>131</sup>I-labeled antibody according to a predetermined dose-escalation scheme based on the amount of radiation received by critical normal organs (i.e., 10, 15, 16.75, 20.25, 23.75, 27.25, and 30.75 Gy). The amount of antibody (expressed in milligrams per kilogram) was selected on the basis of the optimal dose in the trace-labeled biodistribution studies. The amount of <sup>131</sup>I administered was determined from the absorbed-dose estimates (expressed in grays per millicurie) calculated for normal organs from the trace-labeled biodistribution studies (see above). The patients were treated in lead-lined isolation rooms; the antibody was infused from a lead-shielded reservoir with an automatic pump. The patients were kept in isolation until total-body activity decreased to less than 5 mR (1.29 C per kilogram) per hour at 1 m. Autologous purged marrow was reinfused if neutrophil counts fell below 200 per cubic millimeter for two consecutive days provided the total-body activity of <sup>131</sup>I was below 2 mR (0.5 C per kilogram) per hour at 1 m. In some patients, granulocyte-macrophage colony-stimulating factor (250 µg per square meter of body-surface area per day) was administered intravenously daily until the neutrophil count exceeded 1000 per cubic millimeter for two consecutive days. Complete responses were defined as the complete disappearance of all tumor for at least one month, partial responses as 50 to 99 percent regression, and minor responses as 25 to 50 percent regression. Two patients meeting the Cotswold definition of complete response (unconfirmed) were considered to have had complete responses.<sup>11</sup>

### Evaluation of Toxicity

We assessed toxicity with a grading scale devised for marrow transplantation conditioning regimens.<sup>4</sup> This scale does not consider hematologic toxicity and allows greater levels of nonhematologic toxicity than most cooperative-group toxicity scales. The study was terminated when a single, life-threatening (grade 3) or fatal (grade 4) nonhematopoietic toxic event occurred.

### Statistical Analysis

Associations in two-by-two tables were tested with the two-sided Fisher's exact test. Groups of values were compared with Student's *t*-test (for continuous distributions that were approximately normal) or the Mann-Whitney test (for ordinal data).

## RESULTS

### Biodistribution Studies

The clinical characteristics of the 43 patients are listed in Table 2. On average, the patients had received three different therapeutic regimens before being referred to this study. Eighty-four infusions of antibodies trace-labeled with <sup>131</sup>I were administered, and positive tumor imaging was observed in 36 patients (84 percent), including 25 of the 26 patients (96

Table 1. Characteristics of the Monoclonal Antibodies Recognizing B-Lymphocyte Surface Antigens.

ANTIBODY	ANTIGEN	ISOTYPE	IMMUNOREACTIVITY (%) <sup>a</sup>	AVIDITY (M <sup>-1</sup> ) <sup>a</sup>	MANUFACTURER
MB-1	CD37	IgG1	90	3 × 10 <sup>9</sup>	Idec Pharmaceuticals
B1	CD20	IgG2a	80	2 × 10 <sup>8</sup>	Coulter Corporation
IF5	CD20	IgG2a	80	3.7 × 10 <sup>8</sup>	Bristol-Myers Squibb

<sup>a</sup>Measured by the method of Badger et al.<sup>6</sup> with the Daudi cell line.

percent) who received infusions of <sup>131</sup>I-labeled B1. The biodistribution of antibody was favorable (as defined in the Methods section) in 24 of the 43 patients (56 percent). Twelve patients (including eight with large spleens and tumor burdens exceeding 500 ml) demonstrated unequivocal tumor imaging by radioimmunoscinigraphy but did not meet our criterion for favorable biodistribution. Sequential weekly infusions of 0.5, 2.5, and 10 mg of <sup>131</sup>I-labeled antibodies per kilogram demonstrated that the majority of patients achieved a favorable biodistribution after the infusion of 2.5 mg of <sup>131</sup>I-labeled B1 per kilogram, but that a dose of 10 mg per kilogram was required for <sup>131</sup>I-labeled MB-1 (Fig. 1). Subsequently, some patients received only one or two of the three doses and were not given higher levels if a favorable biodistribution was achieved with a lower dose.

### Effect of Tumor Burden and Spleen Size

All five patients with previous splenectomy had a favorable biodistribution, as compared with 17 of 23 patients with a normal-sized spleen and 2 of 15 patients with splenomegaly (*P* < 0.001 for splenomegaly as compared with no splenomegaly). Patients with a favorable antibody biodistribution had an average (±SD) tumor burden of 194 ± 175 ml, as compared with a burden of 1011 ± 954 ml in those who did not (*P* < 0.001). Twenty-three of 31 patients with tumor burdens of 500 ml or less had a favorable biodistribution, as compared with 1 of 12 patients with tumor burdens exceeding 500 ml (*P* < 0.001) (Fig. 2).

### Pharmacokinetics

Serial serum specimens revealed a dose-related prolongation of the serum retention half-time of <sup>131</sup>I-labeled MB-1 (mean, 10.0 ± 5.4 hours after a dose of 0.5 mg per kilogram, 20.8 ± 7.6 hours after a dose of 2.5 mg per kilogram, and 34.5 ± 9.8 hours after a dose of 10 mg per kilogram) but not of <sup>131</sup>I-labeled B1 (mean, 35.5 ± 16.8, 48.2 ± 17, and 48.1 ± 23.3 hours after doses of 0.5, 2.5, and 10 mg per kilogram, respectively). The nonbinding <sup>125</sup>I-labeled control antibody was cleared with a serum half-time of 40.7 ± 14.6 hours. Tumor uptake averaged 0.009 ± 0.003 percent of the injected dose per gram of tumor in the patients with a favorable biodistribution of <sup>131</sup>I-labeled B1, 0.003 ± 0.001 percent in the patients with a favorable biodistribution of <sup>131</sup>I-labeled MB-1 (*P* < 0.01 as com-

Table 2. Characteristics of 43 Patients with B-Cell Lymphoma in Relapse Treated with  $^{131}\text{I}$ -Labeled Antibodies.

CHARACTERISTIC	VALUE*
Median age (yr)	47
Tumor stage	
III	16
IV	27
Histologic appearance†	
Low grade	31 (72)
Intermediate grade	12 (28)
Serum lactate dehydrogenase >250 U/liter	30 (70)
Tumor volume >500 ml	12 (28)
Splenomegaly	15 (35)
Positive tumor imaging‡	36 (84)
Favorable biodistribution§	24 (56)

\*Unless otherwise stated, values given are the number of patients, with percentages given in parentheses.

†There were 18 follicular small-cleaved-cell tumors, 12 follicular mixed small-cleaved-cell and large-cell tumors, 1 diffuse intermediate-cell lymphoma, 6 diffuse small-cleaved-cell tumors, 3 diffuse large-cell tumors, 2 follicular large-cell tumors, and 1 diffuse mixed small-cleaved-cell and large-cell lymphoma.

‡Positive tumor imaging refers to tumors that were clearly discernible on gamma-camera images after the infusion of antibody trace-labeled with  $^{131}\text{I}$  (5 to 10 mCi).

§Patients with a favorable biodistribution were those in whom every assessable tumor site absorbed higher doses of radiation than critical normal organs (liver, kidneys, or lungs).

pared with the value for B1), and  $0.002 \pm 0.002$  percent in the patients with an unfavorable biodistribution (with either antibody).

#### Therapeutic Infusions of $^{131}\text{I}$ -Labeled Antibodies

Twenty-four of the 43 patients had a favorable biodistribution of antibody. Three of these patients did not receive therapeutic infusions because of the development of human antimouse antibodies, one because of insurance disallowal, and one because of the temporary unavailability of antibody. Table 3 summarizes the doses of antibody and radioiodine administered to the 19 patients who were treated. The doses were individualized so that each patient received the dose of protein found to yield the most favorable biodistribution in the trace-labeled-antibody studies and the  $^{131}\text{I}$  dose calculated to deliver the target level of  $^{131}\text{I}$  activity to the normal organ receiving the highest dose of radiation. In 17 of the 19 patients, the lung was the normal organ receiving the dose-limiting radiation exposure. Tumor sites were estimated to receive between 10.1 and 91.5 Gy, with lower doses absorbed by normal organs in all patients (Table 4).

#### Toxicity

The infusions of antibody trace-labeled with  $^{131}\text{I}$  were well tolerated. Myelosuppression ensued after all therapeutic infusions; 15 patients received autologous marrow reinfusions 13 to 31 days later. At the two lowest therapeutic doses, the nadirs of the platelet and leukocyte counts occurred 3 to 4 weeks after infusion, whereas at the two highest doses, the nadirs occurred after 10 to 14 days. Recovery of the neutrophil count

to 500 per cubic millimeter or higher occurred a median ( $\pm$ SD) of  $22 \pm 9$  days after marrow infusion, whereas platelet recovery was more variable, occurring a median of  $20 \pm 27$  days after marrow infusion (range, 3 to >107). Six minor infections (two cases of herpes simplex stomatitis, two cases of *Clostridium difficile* colitis, and two catheter infections caused by *Staphylococcus epidermidis*) and three serious infections (*S. aureus* septicemia, *Pneumocystis carinii* pneumonia, and hepatosplenic candidiasis) occurred, but all resolved with antibiotic therapy.

Nonhematologic toxic effects included mild nausea (79 percent), fever (74 percent), elevated serum concentrations of thyrotropin (for which thyroxine was given) (42 percent), mild alopecia (21 percent), hyperbilirubinemia (37 percent; bilirubin range, 1.2 to 3.9 mg per deciliter [21 to 67  $\mu\text{mol}$  per liter]), transient serum alanine aminotransferase elevations (42 percent; alanine aminotransferase range, 41 to 242 U per liter), and mild transient serum creatinine elevations associated with empirical amphotericin B therapy (33 percent; creatinine range, 1.3 to 2.3 mg per deciliter [115 to 203  $\mu\text{mol}$  per liter]). The severity of these effects correlated with the dose of radioimmunotherapy administered. Patients treated with doses that delivered 23.75 Gy or less to normal organs had few nonhematologic toxic effects, whereas all patients who received the two highest doses (Table 3) had marked asthenia, nausea, diarrhea, and anorexia, as well as single occurrences of parotitis and ileus requiring

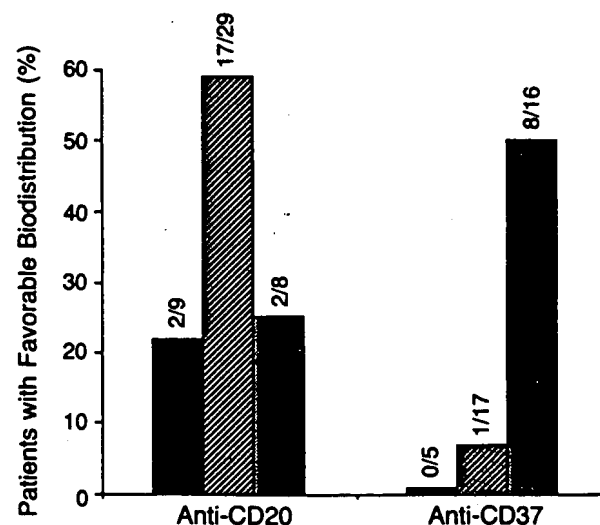


Figure 1. Effect of the Dose of Antibody Protein Infused on Biodistribution.

The percentage of patients given doses of 0.5 mg per kilogram (black bars), 2.5 mg per kilogram (hatched bars), or 10 mg per kilogram (stippled bars) of anti-CD20 antibodies (B1 or 1F5) or anti-CD37 antibody (MB-1) trace-labeled with  $^{131}\text{I}$  who had a favorable antibody biodistribution is shown. The number above each bar is the number of patients with favorable biodistribution divided by the number of patients given that antibody at that dose.

Several patients received infusions of each type of antibody.

nasogastric suctioning. Life-threatening hemorrhagic pneumonitis and congestive cardiomyopathy developed in one patient two months after treatment with a dose that delivered 27.25 Gy to the lungs. The patient was admitted to the intensive care unit for continuous positive airway-pressure ventilation with 100 percent oxygen for three days and therapy with digoxin, diuretics, hydralazine, and nitrates. Severe postural hypotension requiring the administration of dopamine developed in another patient after treatment with a dose that delivered 30.75 Gy to the lungs. Both patients subsequently recovered. One patient had a superficial bladder carcinoma 26 months after radioimmunotherapy and underwent transurethral resection, with complete removal of the tumor. Fourteen of the 43 patients (33 percent) had serum antimouse antibodies 2 to 76 weeks (median, 5) after exposure to the murine antibodies. This phase 1 trial was terminated after the development of cardiopulmonary complications in the two patients described above.

#### Responses to Therapy

Sixteen of the 19 patients had complete remissions, 2 had partial responses, and 1 had a minor response (40 percent reduction in the size of the tumor without regrowth for 18 months). The median duration of response exceeded 11 months for patients receiving  $^{131}\text{I}$ -labeled B1 and 7 months for all patients. At the most recent evaluation, nine patients remained in continuous complete remission without further therapy, including one patient treated almost five years previously. Ten patients had relapsed after remissions lasting

Table 3. Treatment Characteristics of 19 Patients Receiving High-Dose Radioimmunotherapy.

PATIENT No.	DOSE*	ANTI-BODY	PROTEIN DOSE	$^{131}\text{I}$ DOSE	TIME FROM THERAPY TO MARROW TRANSPLANTATION†	RESPONSE TYPE	DURATION
					days		
1	10.00	MB-1	2.5	242	ND	Complete	6
2	10.00	MB-1	10	482	ND	Complete	4
7	10.00	MB-1	10	371	ND	Complete	12
8	15.00	MB-1	10	234	31	Complete	>53
10	15.00	IF5	2.5	608	27	Partial	2
13	15.00	MB-1	10	628	15	Complete	12
16	16.75	MB-1	10	448	14	Complete	7
18	16.75	B1	2.5	280	ND	Complete	>36
22	16.75	B1	2.5	330	22	Minor	18
23	20.25	B1	0.5	549	27	Complete	6
24	20.25	B1	10	559	18	Complete	>24
26	20.25	B1	2.5	556	14	Complete	>20
29	23.75	B1	2.5	376	16	Partial	5
31	23.75	B1	2.5	443	21	Complete	>16
32	23.75	B1	2.5	560	13	Complete	>15
33	27.25	B1	2.5	738	15	Complete	5
36	27.25	B1	2.5	777	18	Complete	>8
40	27.25	B1	2.5	560	14	Complete	>4
41	30.75	B1	2.5	513	16	Complete	>3

\*The estimated dose of radiation absorbed by the normal organ (liver, kidneys, or lungs) receiving the highest dose of radiation.

†ND denotes bone marrow transplantation not done.

2 to 18 months (Table 3). In five patients, the relapses were confirmed by biopsy, and in all five the expression of target antigen in the tumor tissue was unchanged. Sixteen of the 19 patients were alive after a median follow-up of more than 26 months (Table 3). The overall median survival for these 19 patients exceeded 21 months.

#### DISCUSSION

Five major observations emerged from this study. First, high doses of  $^{131}\text{I}$ -labeled anti-B-cell antibodies could be successfully administered to patients with B-cell lymphoma in relapse if autologous marrow was reinfused. Second, therapy with  $^{131}\text{I}$ -labeled B1 was limited to doses delivering less than 27.25 Gy to the lungs; further dose escalation was limited by cardiopulmonary toxicity. Third, patients without splenomegaly and with tumor burdens of less than 500 ml were more likely to have a favorable antibody biodistribution than patients with splenomegaly and a larger tumor burden. Fourth, patients with a favorable biodistribution when given a dose of antibody trace-labeled with  $^{131}\text{I}$  had an 84 percent rate of complete remission and an 11 percent rate of partial remission after the administration of antibody labeled with therapeutic doses of  $^{131}\text{I}$ . Fifth, the median duration of the tumor responses exceeded 11 months after therapy with  $^{131}\text{I}$ -labeled B1 (anti-CD20).

The results of the phase 1 dose-escalation trial to define the dose-limiting nonhematologic toxicity of radiolabeled antibodies suggest that cardiopulmonary

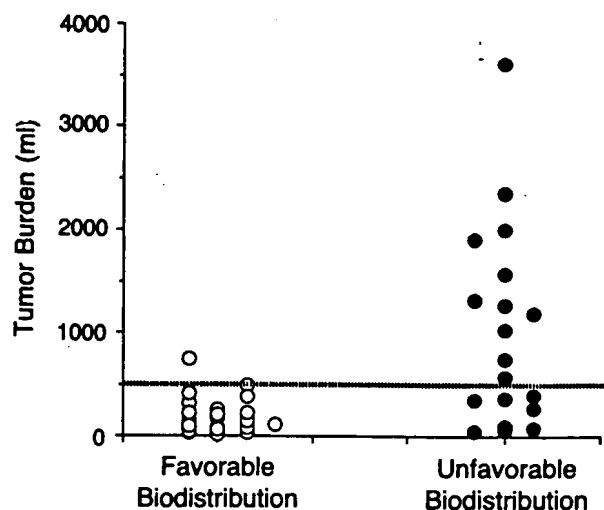


Figure 2. Effect of Tumor Burden on  $^{131}\text{I}$ -Labeled Antibody Biodistribution.

Patients with a favorable antibody biodistribution (open circles) and those with an unfavorable antibody biodistribution (solid circles) are plotted according to tumor burden as estimated by computed tomography ( $P < 0.001$ ). (Because of similar values, some circles overlap.) Twenty-three of 31 patients with tumor burdens of 500 ml or less had a favorable biodistribution, as compared with 1 of 12 patients with tumor burdens exceeding 500 ml.

Table 4. Estimated Doses of Radiation Absorbed by the Tumors and Normal Organs.

SITE	ABSORBED DOSE OF RADIATION  Gy	ABSORBED-DOSE RATIO*	
		RANGE	MEAN $\pm$ SE
Tumor	10.1-91.5	—	—
Lungs	6.5-31.0	1.1-4.2	1.8 $\pm$ 0.2
Liver	3.8-19.3	1.4-5.1	3.0 $\pm$ 0.3
Kidneys	5.4-21.6	1.7-7.0	3.4 $\pm$ 0.3
Marrow	1.0-6.4	3.6-22.4	10.2 $\pm$ 1.1
Total body	1.0-5.7	4.5-20.2	10.4 $\pm$ 1.0

\*The ratio of the dose absorbed by the tumor to that absorbed by the organ. Quantitative serial gamma-camera imaging and tumor biopsies provided the biodistribution data used to estimate the doses of radiation absorbed by the tumors and normal organs after infusions of  $^{131}\text{I}$ -labeled antibodies.

and gastrointestinal toxicity will prevent the routine administration of doses of  $^{131}\text{I}$ -labeled antibodies that deliver more than 27.25 Gy to normal organs. Myelosuppression was severe, but it was manageable with autologous marrow reinfusion, treatment with granulocyte-macrophage colony-stimulating factor, antibiotic therapy, and transfusions. Our study differs from most other radioimmunotherapy trials in that we defined dose levels on the basis of estimated doses of radiation absorbed by normal organs rather than fixed doses of radionuclide determined by body weight or surface area. We used this approach because the biodistribution of antibody varied considerably from patient to patient, suggesting that dose-limiting toxic effects would correlate better with the radiation doses absorbed by critical normal organs than with a weight-based dose of radioiodine. In spite of the fact that variable absolute doses of  $^{131}\text{I}$ -labeled antibodies (measured in millicuries per kilogram) were required to achieve the target doses of radiation (measured in grays) among patients within a dose-level cohort (Table 3), the severity of toxic effects among patients in each cohort was concordant. The consistency of these results suggests that individualized calculation of doses based on antibody biodistribution and pharmacokinetics may be necessary for optimal trial design.

Patients with tumor burdens exceeding 500 ml or with massive splenomegaly rarely met our stringent criteria for radioimmunotherapy, even though positive tumor imaging was often observed. Similar effects of tumor burden and splenomegaly have been reported by others,<sup>12-15</sup> presumably reflecting the trapping of B-cell antibodies by the spleen as well as limited penetration of radiolabeled immunoconjugates into large tumor masses. The B1 (anti-CD20) antibody was superior to MB-1 (anti-CD37) because B1 caused less toxicity, achieved a favorable biodistribution with smaller doses (Fig. 1), and was more slowly internalized and degraded by tumor cells,<sup>16</sup> presumably contributing to the longer serum half-time.

The overall rate of response (95 percent), rate of complete response (84 percent), and median duration

of response (>11 months for patients treated with  $^{131}\text{I}$ -labeled B1) in this trial are very encouraging. We attribute the high rate of tumor regression to a combination of three factors: the tumoricidal effects of the monoclonal antibodies themselves,<sup>17</sup> nonspecific total-body irradiation from the large doses of  $^{131}\text{I}$  administered, and selective targeting of radioiodine by B-cell-specific antibodies. Our approach has allowed us, on average, to deliver 10 times as much cytotoxic radiation to tumor sites as to the whole body and 2 to 3 times as much as to critical organs (Table 4), suggesting an advantage for this approach as compared with external-beam irradiation.<sup>18</sup>

Although others have published promising results of radioimmunotherapy for lymphomas,<sup>13-15,19-26</sup> the lower levels of radioactivity used resulted in lower overall response rates (29 to 55 percent), lower rates of complete response (3 to 33 percent), and shorter durations of response (median, <6 months) than in our high-dose trial. In the only other published trial of myeloablative radioimmunotherapy, 17 patients with Hodgkin's disease in relapse were treated with yttrium-90-labeled polyclonal antiferritin antibodies; 7 patients had complete responses, and 4 had partial responses.<sup>14</sup> Since the highest rates of complete response to radioimmunotherapy were in the two trials that used myeloablative radiation doses, we suggest that this high-dose approach warrants further investigation.

*Note added in proof:* Since this report was submitted for publication, Kaminski et al.<sup>27</sup> have reported responses in six of nine patients who received lower doses of  $^{131}\text{I}$ -labeled B1 antibody.

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